Statistical analysis plan (SAP)

Administrative information:

Trial title	Plantar fasciopathy and the effectiveness of radial extracorporeal shock wave therapy, physical training or usual care.
Trial registration number	NCT03472989
REC no	2017/1325
SAP version and date	This is SAP version 1, dated 21.02.23
Protocol version	This document has been written based on information contained in the study protocol (1).
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1.0 Introduction

This document describes the planned statistical analyses to be performed for the clinical trial: "The effectiveness of radial extracorporeal shock wave therapy (rESWT), sham rESWT, standardised exercise program or usual care for patients with plantar fasciopathy". It is intended to supplement the study protocol (1).

The overall purpose of this study is to evaluate whether radial extracorporeal shock wave therapy (rESWT), sham-rESWT or a standardised high-load strength training program is more effective on change in heel pain than usual care in the treatment of plantar fasciopathy.

1.2 Research hypothesis

Null hypothesis

H_0: There is no difference between rESWT, sham-rESWT and a standardised exercise programme on change in heel pain (primary outcome) and functioning (secondary outcomes) compared to usual care in the treatment of plantar fasciopathy at 6 months follow-up (and secondary outcomes at 12 months follow-up).

Alternative hypothesis

- H_1: There is a difference between rESWT and usual care on change in heel pain (and secondary outcomes) at 6 months follow-up (and secondary outcomes at 12 months follow-up).
- H_2: There is a difference between sham-rESWT and usual care on change in heel pain (and secondary outcomes) at 6 months follow-up (and secondary outcomes at 12 months follow-up).
- H_3: There is a difference between the standardised exercise programme and usual care on change in heel pain (and secondary outcomes) at 6 months follow-up (and secondary outcomes at 12 months follow-up).

2.0 Study methods

2.1 Trial design

The study is designed as a double- blind, randomized, sham-controlled trial, with four parallel groups.

2.2 Randomization

Eligible patients were randomized in a 1:1 ratio. Treatment allocation was done by a computer generation randomization schedule with blocks of 8.

2.3 Sample size

The sample size was based on the primary outcome measure Numeric Rating Scale (NRS) at 6 months, for a comparison between two of the treatment groups using a two-sided t test. With a statistical test power of 90%, a significance level of 5 %, an assumed difference of 2 of NRS (2), estimated standard deviation (SD) of 2.7 (based on previous clinical data from the Department of Physical Medicine and Rehabilitation) and a dropout of 20%, the sample size was estimated to be 200, with 50 in each group.

2.4 Endpoints/outcome

2.4.1 Primary outcome measure

Numeric rating scale (NRS) is a patient reported pain intensity scale ranging from 0 (no pain) to 10 (worst possible pain) (3). We asked the patients to rate their pain in activity the last week, and measured change in NRS between baseline and 6 months follow-up.

2.4.2 Secondary outcome measures

Foot Function Index, revised, short form (FFI-RS) is a region specific patient reported outcome measure. FFI-RS consists of 34 questions. Scoring is from 0-100 where lower score indicate better foot health status (4). Measured after 6 and 12 months.
RAND- 12 is a generic PROM measuring health related quality of life. RAND-12 has 12 items, were six create the Mental Health Composite (MHC) and the remaining the Physical Health Composite (PHC). Scoring is from 0-100, were higher score indicate better health related quality of life (5). Measured after 6 and 12 months.
Numeric rating scale (NRS) (in rest the last week). Measured after 6 and 12 months.
Numeric rating scale (NRS) (in activity the last week). Measured after 12 months.
Patient Global Impression Of Change (PGIC) scale is 7-point scale ranging from "very much improved" to "very much worse". The questioning is “Compared to the start of the study what is your general health status today”(6). Measured after 6 and 12 months.

2.5 Timing of outcome assessments

	Enrolment	Allocation	Interventions	**Follow-up**	**Follow-up**	**Follow-up**
Timepoint	0	0	0-3 months	**3 months**	**6 months**	**12 months**
Assessments:						
Baseline variables 1)	X					
NRS 2)	X			X	X	X
FFI-RS 3)	X			X	X	X
RAND-12 4)	X			X	X	X
PGIC 5)	X			X	X	X
Other variables 6)				X	X	X
Clinical examination, ultrasound 7)	X				X	X

1)Baseline variables: age, sex, relationship status, education, work situation, sick leave, duration of symptoms, previous treatment, previous use of radial extracorporeal shock wave treatment, use of pain medication, physical activity, smoke/non-smoker, expectation of change in foot pain, which treatment he/she hopes to get in the trial. In addition the physician register sick leave status and if the sick leave is because of foot pain. 2) NRS: Numeric Rating Scale. 3)FFI-RS: Foot Function Index revised short form. 4) RAND-12: RAND-12 Health Status Inventory.5)PGIC: Patient Global Impression of Change. 6) Other variables: Use of foot orthosis, side effects of treatment, use of other treatment modalities, use of pain medication. 7) Clinical examination includes palpation of the ankle and foot including the insertion of the

plantar fascia, weight-bearing ankle dorsiflexion motion, calf-raise test, measurement of calf circumference. In addition and only at inclusion: Measure of height, weight, body mass index, measure of passive range of motion in the ankle joint.

The ultrasound measures include thickness in millimeter, hypo echogenicity (presence/no presence), neovascularization (presence/no presence) and calcification (presence/no presence).

At baseline the patients completed the patient- reported outcome measures (PROMs): Numeric Rating Scale (NRS) (primary endpoint), RAND-12 Health status inventory (RAND-12) and Foot Function Index revised short form (FFI-RS) (secondary outcomes). In addition they completed a questionnaire including patient characteristics, anthropometric data and the duration of symptoms.

After 3 months, the patients received a letter with the same PROMs and in addition the Patients`Global Impression of Change Scalge (PGIC), which they filled out and returned. In addition they filled out a questionnaire regarding use of foot orthosis, side effects of treatment, use of other treatment modalities, and use of pain medication.

The patients were asked to complete the same PROMs and questionnaire as stated above prior to clinical examination and ultrasound at the 6- and 12 months follow-up visit.

At baseline, 6 months and 12 months follow-up the patients had a clinical examination including ultrasound.

3.0 General considerations

3.1 Adherence and protocol deviations

The number and proportion of patients that received the intervention they were randomized to will be presented. The following are pre-defined major protocol deviations regarded to affect the efficacy of the intervention:

- Compliance of interventions: For the rESWT, the patients have to complete at least 2 out of 3 sessions. For the training programme the patients must have attended at least 6 out of 8 sessions with the physiotherapist or at least have completed 30 of 36 exercise sessions.
- Timing of follow-up visits: Patients not completing post baseline follow-up within +/- 4 weeks for the 3 months follow-up, +/- 4 weeks for the 6 month follow- up, and +/- 8 weeks for the 12 month follow- up.

3.2 Analysis populations

We define the following patient population in this trial:

- Intention- to- treat analysis set: All patients that have been randomized will be analyzed according to the group they were originally assigned, regardless what treatment (or not) they received.
- Per protocol analysis set: All patients that were randomized, received treatment according to protocol without deviations (as described for in “compliance of

interventions" and "timing of follow-up visits" above) were analyzed according to the treatment they were randomized to.

3.3 Statistical Framework

Superiority hypothesis testing will be performed to test the effectiveness of the interventions compared to usual care, according to the null hypothesis as stated above. Superiority of rESWT group, sham-rESWT group or exercise group over usual care will be claimed if the two-sided p value in the test comparing the change from baseline to 6 months in NRS score is less than 5 %. This protocol is designed to address a single primary endpoint; measure of heel pain using NRS. A difference in the effect of the interventions will be claimed if null hypothesis is rejected, that is if the two-sided p- value is less than 5%.

3.4 Statistical interim analyses and stopping guidance

There will be no interim analyses in this trial.

If severe medical events occur, the manager of the department have access to unblind that particular patient.

3.5 Timing of final analysis

The analysis is timing stratified by planned length of follow-up. When all patients have completed a minimum of 6 months follow- up the analysis of the primary outcome will be performed. When all patients have completed a minimum of 12 months follow-up the secondary analysis will be performed.

3.6 Baseline patient characteristics

Baseline characteristics of the study population will be summarized separately with each randomized group. For continuous variables, means and standard deviations will be presented, unless the variable has a highly skewed distribution, in which case, medians 25^{th} and 75^{th} percentiles will be presented. For categorical (binary or ordinal) variables, the number and percentage of participants within each category will be presented. For each variable (continuous or categorical), the percentage of missing values will be reported.

4.0 Analysis methods

4.1 Statistical methods

The results of the trial will be presented following the standard CONSORT recommendations (7).

A CONSORT diagram will be used to show patient flow with number of patients considered and total numbers randomized.

All calculated p-values will be two-sided and compared to a 5% significance level. If a p-value is less than 0.05, the null hypothesis in the test will be rejected. Efficacy estimates for the comparison of treatment interventions will be presented with two-sided 95% confidence intervals.

P-values will be rounded to three decimal places. P-values less than 0.001 will be reported as <0.001 in tables. There will be no adjustment to secondary outcomes for multiple testing.

4.1.1 Analysis of primary outcome

The primary outcome is change in heel pain score (NRS) during activity last week from baseline to 6 months, will be analyzed using linear mixed effects model. The model will include fixed effects for time, and treatment x time interaction. The main effect of treatment group will be removed from the model to adjust for potential differences in the score at baseline. A random intercept will be used. Based on this model, the primary efficiacy outcome of between-group differences in changes from baseline to 6 months follow-up will be estimated. This model allows for comparison between rESWT, sham-rESWT and a standardised exercise programme compared to usual care.The primary effect analysis will use the intention- to treat population.

4.1.2 Analysis of secondary outcomes

For secondary outcomes, assessed at multiple time points (baseline, 3, 6 and 12 months) will be analysed by using a linear mixed effect model approach as described in section 4.1.1 on both the intention-to treat population and the per protocol population

4.2 Missing data

Missing items on FFI-RS and RAND-12 will be imputet if less than 25% of the answers are missing using Predictive Mean Matching. If more than 25% of the items are missing, no score will be computed.

Missing data for repeated measured continuous endpoints will be implicitly handled by the linear mixed-effects models under the assumption of missing at random observations; thus no imputation is required.

4.3 Additional analyses

We will apply a multivariable logistic and linear regression analysis to explore predictive factors as demographics, clinical and ultrasound findings for primary and secondary outcomes. Model building will be done in a way that is appropriate for the given sample sizes, by restricting the number of potential predictive factors and considering shrinkage methods to stabilise predictions.

4.4 Adverse Events

Any complications and adverse events were continuously registered.

4.5 Statistical software

All statistical analysis will be done using SPSS version 28 or STATA version 17.

5.0 References

1. Heide M, Mørk M, Røe C, Brox JI, Fenne Hoksrud A. The effectiveness of radial extracorporeal shock wave therapy (rESWT), sham-rESWT, standardised exercise programme or usual care for patients with plantar fasciopathy: study protocol for a double-blind, randomised, sham-controlled trial. Trials. 2020;21(1):589.
2. Farrar JT, Young JP, Jr., LaMoreaux L, Werth JL, Poole MR. Clinical importance of changes in chronic pain intensity measured on an 11-point numerical pain rating scale. Pain. 2001;94(2):149-58.
3. Ferreira-Valente MA, Pais-Ribeiro JL, Jensen MP. Validity of four pain intensity rating scales. Pain. 2011;152(10):2399-404.
4. Budiman-Mak E, Conrad KJ, Mazza J, Stuck RM. A review of the foot function index and the foot function index - revised. J Foot Ankle Res. 2013;6(1):5.
5. Johnson JA, Maddigan SL. Performance of the RAND-12 and SF-12 summary scores in type 2 diabetes. Qual Life Res. 2004;13(2):449-56.
6. Dworkin RH, Turk DC, Farrar JT, Haythornthwaite JA, Jensen MP, Katz NP, et al. Core outcome measures for chronic pain clinical trials: IMMPACT recommendations. Pain. 2005;113(1-2):9-19.
7. Moher D, Hopewell S, Schulz KF, Montori V, Gøtzsche PC, Devereaux PJ, et al. CONSORT 2010 explanation and elaboration: updated guidelines for reporting parallel group randomised trials. Bmj. 2010;340:c869.